## REMARKS/ARGUMENTS

Reconsideration of this application is respectfully requested.

The allowance of claims 6, 7, 20 and 21 is noted.

Claims 17-19 stand rejected under 35 USC 102(b) as allegedly being anticipated by USP 6,127,142. The rejection is traversed.

Claim 17, from which claims 18 and 19 depend, is drawn to an isolated polypeptide that exhibits aspartic protease activity and that comprises an N-X-T glycosylation site. The claim specifically requires that the aspartic protease be a chymosin.

USP 6,127,142 relates to a method for deglycosylating an aspartic protease from *Rhizomucor miehei* (EC 3.4.23.23 Mucor rennin), which is not a chymosin (EC 3.4.23.4). Indeed, the Examiner acknowledges this to be the case. Accordingly, the novelty of the claims over the reference is clear.

In maintaining the rejection, the Examiner refers to the statement at column 6, lines 38-41 of the cited patent:

> Thus, as an example, a suitable milk clotting enzyme should ideally have an activity ratio similar to or close to that of pure calf chymosin for milk clotting activity at two different pH values such as 6.0/6.5 or 6.5-7.0.

The Examiner contends that this sentence implies that bovine chymosin is acceptable to use as the protease. This assertion ignores the fact that the patent relates to a method of deglycosylating a protease that is not a chymosin. The statement quoted above does not alter that fact – the quoted passage merely indicates a target activity ratio for the deglycosylated *Rhizomucor miehei* aspartic protease. This is clear from the sentence that follows at column 6, lines 43-48:

> Thus, it was found during the experimentation leading it the present invention that treatment of certain *Rhizomucor miehei*

> aspartic proteases having a relatively high pH dependency (ie. activity ratios above that of chymosin) with Endo H reduced the pH 6.0/6.5 or the 6.5/7.0 activity ratios to values closer to that of calf chymosin.

(It should be noted that "activity ratio" is not the same as "activity".)

It will be clear from the foregoing that USP 6,127,142 does not anticipate the claimed invention. Furthermore, the cited patented would not have rendered the invention obvious. The patent teaches that homologous *Rhizomucor miehei* aspartic protease acquires significantly enhanced milk clotting activity when it is deglycosylated, likewise, heterologous *Rhizomucor miehei* aspartic protease produced in *A. oryzae*. The aspartic protease from *Rhizomucor miehei* is not a chymosin. Thus, nothing in the patent teachings could have suggested the claimed polypeptide exhibiting aspartic protease activity and comprising a N-X-T glycosylation site since the claims require that the aspartic protease be a chymosin.

In view of the above, it is again submitted that USP 6,127,142 does not anticipate claims 17-19. Further, the reference would not have rendered the claims obvious. Reconsideration is requested.

Claims 1-5, 8, 12-15, 17-19 and 22 stand rejected under 35 USC 103 as allegedly being obvious over USP 5,800,849 in view of Kasturi et al and USP 6,127,142. Withdrawal of the rejection is in order for the reasons that follow.

Applicants pointed out in the prior Amendment that underlying the present invention was a desire to provide a method for more efficiently producing aspartic protease in a host organism. Applicants submit that the cited combination of art would in no way would have suggested addressing that problem by modifying the polynucleotide sequence to encode an (extra) N-X-T glycosylation site in the aspartic protease amino acid sequence, and subsequently expressing the

sequence. The Examiner's comments suggest that she does not disagree with Applicants in this regard (see page 5 of the Action, lines 10-15) but that she is of the view that some other advantage "would flow naturally from following the suggestion of the prior art." Conspicuous by its absence, however, is any clear statement from the Examiner as to what that other advantage might be. The Examiner is again urged to provide Applicants with a clear explanation as to the nature of the "other" advantage that the Examiner believes "would naturally flow from following the suggestion of the prior art." Absent that explanation, Applicants are not properly positioned to respond to the rejection.

USP 5,800,849 relates to a process for producing cheese in improved yield. The process comprises adding to milk a recombinant aspartic protease derived from *Rhizomucor miehei* to effect clotting. The reference indicates at, column 2, lines 57-60, that increased glycosylation was found to be surprisingly advantageous. Specifically, it is stated that:

> The extent of glycosylation of the recombinant aspartic protease has surprisingly been found to be higher than the glycosylation of the aspartic proteases obtained from naturally occurring Rhizomucor strains.

As the Examiner acknowledges, the reference does not teach the glycosylation site as being N-X-T. The higher degree of glycosylation was obtained by expression of the Rhizomucor gene in Aspergillus/Trichoderma host cells.

Kasturi et al reports the results of studies designed to compare "the impact of the Xaa residue in Asn-Xaa-Ser sequons with that of Asn-Xaa-Thr sequons to define further the protein sequences that control N-linked core glycosylation" (page 415, right column, bottom of only full paragraph). Rabies virus glycoprotein (RGP) was the primary model system used.

USP 6,127,142 relates to at least partially deglycosylated microbially-derived milk clotting enzymes, particularly to aspartic proteases derived from *Rhizomucor miehei* having improved milk clotting activity. It is indicated at column 2, line 46, that decreased glycosylation was surprisingly advantageous. Specifically, it is stated that:

> It has now surprisingly been found that homologous *Rhizomucor miehei* aspartic protease, contrary to what has been stated in the prior art, acquires a significantly enhanced milk clotting activity when it is deglycosylated, and furthermore, that the milk clotting activity of heterologous *Rhizomucor miehei* aspartic protease as produced in *Aspergillus oryzae* ... is enhanced significantly by deglycosylation.

On page 6 of the September 18, 2007 Action, the Examiner makes reference to column 3, lines 38-41 of USP 6,127,142 and contends that this passage implies "that bovine chymosin is acceptable to use as the protease". Appliants explain above, in response to the rejection of claims 17-19, why this comment reflects a misunderstanding on the Examiner's part of the reference teachings .

Summarizing, USP 5,800,849 teaches that "glycosylation of the aspartic protease can give an increase in cheese yield" (column 1, lines 25-27 – underlining added), Kasturi et al provides a comparison of "the impact of the Xaa residue in Asn-Xaa-Ser sequons with that of Asn-Xaa-Thr sequons to define further protein sequences that control N-linked core glycosylation (p. 415, right column, bottom only full paragraph) and USP 6,127,142 teaches that homologous *Rhizomucor miehei* aspartic protease acquires significantly enhanced milk clotting activity when it is deglycosylated, likewise heterologous *Rhizomucor miehei* aspartic protease produced in *Aspergillus oryzae*.

As pointed out above, the Examiner's comments at page 5 of the Action (lines 10-15) suggest that some advantage "would flow naturally from following the suggestion of the prior

art." The Examiner is requested to identify what suggestion she believes to be provided by these disparate teachings and what advantage she believes flows therefrom so that Applicants will be properly placed to respond. Thus far, the only comment the Examiner has provided appears on page 6 of the September 18, 2007 Action, third paragraph, where the Examiner refers to "[t]he ordinary skilled artisan, desiring to use a N-X-T glycosylation site in chymosin..." (underlining added). Respectfully, the Examiner's explanation as to why the "skilled artisan" would have desired to use a N-X-T-glycosylation site in chymosin is not consistent with the teachings of the cited art, including the teaching of USP 6,127,142 of significantly enhanced clotting activity associated with deglycosylated aspartic protease.. It was Applicants, not the art, who taught the advantage of such use.

Applicants again submit that the rejection is clearly based on improper hindsight-based reasoning. Nothing in the citations would have suggested their combination and nothing in the combination (even if made) would have suggested the present invention.

Reconsideration is requested.

Claims 9-11 and 23 stand rejected under 35 USC 103 as allegedly being obvious over USP 5,800,849, Kasturi et al, USP 6,127,142 and Korman et al. Withdrawal of the rejection is in order for the reasons that follow.

Claims 9-11 are dependent claims directed the production of the protease as a fusion protein, and 23 is directed to the use of Aspergillus host organisms.

In the Amendment filed February 19, 2008, Applicants indicated that the Examiner's position was not understood. Unfortunately, Applicants do not find any clarification in the present Action.

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Applicants again submit that nothing in the references would have provided the motivation necessary to arrive at the present invention. The deficiencies of USP 5,800,849, Kasturi et al and USP 6,127,142 are discussed above. Korman et al adds nothing that would have cured those failings or brought one skilled in the art closer to the present invention. It is only with the benefit of the present invention that the citations would have been combined and their combination, even if made, would not have suggested the subject matter of the instant claims. Accordingly, reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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